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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/523,809	03/13/2000	Michael P. Murphy	686.03.498CON	6553

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EXAMINER	
KAUSHAL, SUMESH	

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1636	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No. 09/523,809	Applicant(s) MURPHY ET AL.	
	Examiner Sumesh Kaushal Ph.D.	Art Unit 1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 10/5/01 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *05 October 2001*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *none*.

Claim(s) objected to: *none*.

Claim(s) rejected: *1-30*.

Claim(s) withdrawn from consideration: *none*.

8.☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

Continuation of 5. does NOT place the application in condition for allowance because claims 1-30 stand rejeacted under 35 USC 112(2) and 35 USC 103 for the same reasons of record as set forth in the earlier official action mailed on the 07/03/01 and as repeated below:

Claim Rejections - 35 USC ' 112

Claims 1-30 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the same reasons of record as set forth in the official action mailed on 07/03/01.

The applicant argues that exogenous matrix components are matrix components not produced by the cultured cell but are introduced by other means. Thus the matrix is completely cell-synthesized and assembled by culturing the cells (response, page e, ¶ 3). However, this is not found persuasive because it is unclear what is the nature (chemical or biological structure) of "exogenous matrix components". Similarly, it is unclear what is encompassed by "synthetic members". The broadest reasonable interpretation of a synthetic member encompass any non-naturally occurring polymer and any and all types of tissue supports.

Claims 7 and 21 are unclear as to the metes and bounds of a culture medium containing "no non-human components". The applicant argues that "no non-human component" are component without the use of undefined or non-human-derived biological components such as bovine serum or organ extract. However, this is not found persuasive because it is still unclear does this include any chemical or protein, to include essential and non-essential amino acids, which are not produced in the human body or required for its proper functioning?

Claims 1-18, 28 and 30 are unclear as to the metes and bounds of cultured "under conditions to produce a layer of extracellular matrix". The applicant argues that the specification clearly describes the conditions to produce a layer of extracellular matrix (response, page 4, ¶ D). However, this is not found persuasive because it is unclear what are the conditions that lead to a layer of extracellular matrix. The specification only teaches the secretion of extracellular matrix in tissue culture media.

Claim Rejections - 35 USC ' 103

Claims 1-3, 6-12, and 19-27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Bell, E. (US Patent 4,485,096), Parenteau et al (US Patent 5,712,163), Sand, BJ (US Patent 5,618,284) and Holbrook et al (1993) and Biegel et al (1994) for the same reasons of record as set forth in the official action mailed on 07/03/01.

The applicant argues that the patentable distinction between Bell and instant invention is that Bell requires the use of hydrated lattice that contain an exogenous matrix component and does not teach the use of chemically defined media (response, page 6, ¶ 1). Applicant further argues that Parenteau does teach a chemically defined cell culture medium but does not teach or suggest instantly claimed invention. The applicant further argues that one would not be motivated to combine Parenteau's reference with Bell in order to culture cells without collagen because Plrenteau would suggest use of collagen and not its absence as being advantageous (response, page 6). The applicant further argues that the ability of fibroblasts cells to produce layer extracellular matrix which is synthesized and assembled by cultured fibroblasts in the absence of exogenous matrix component or synthetic members was unexpected (response, page 7, ¶ 2). The applicant further argues that Sand and Holbrook states what is know in the art regarding human type-I collagen and dermal matrix of connective tissue respectively (response, page 7, ¶ 3-4). The applicant further argues that Biegel does not describe coating transwell filters with hydrated collagen gels then culturing endothelial cells. The applicant concluded that instant invention as claimed is not rendered obvious in view of cited prior art of record.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The

applicant fails to consider the combined teaching of the reference cited herein in entirety. The combination and modification of the teachings of the prior art clearly suggested the claimed invention.

In this case, Bell, E teaches the use *in vitro* of human foreskin and dermal fibroblasts cultured in Falcon bacteriological dishes comprising McCoy's 5a medium, Fetal Calf Serum, NaOH, and a collagen solution to form a contractable, transplant tissue and wherein a layer of keratinocytes may be added *in vitro* (claims 15 & 16; and Example 1, col 8, lines 39-55, col 3, lines 28-30). Bell also teaches the method of tissue transplantation in guinea pigs and rats (e.g. Examples 10 and 11).

Parenteau et al teach the use of a chemically defined cell culture medium, (see columns 10-16) which by definition are absent of undefined proteins from protein supplements such as serum, and wherein the cell culture systems comprise said cell culture medium and a substrate for the cells, such as glass or plastic, and in the absence of exogenous matrix components or synthetic membranes which resulted in the prolonged growth and differentiation of cells, such as keratinocytes,(e.g. col 1, lines 35-55, claims 20 and 24). Furthermore, **Parenteau clearly teaches the culturing of human karatinocytes on plates NOT coated with collagen** (col.24, example-5). Parenteau et al also teach the method of producing skin equivalents grafts in vitro utilizing keratinocytes and dermal (fibroblast) equivalents (example 6, col 25, line 61-col 26, line 14), and the use of a sequential two culture medium process in the absence of a substrate which showed only a slight decrease in plating efficiency in comparison to those that were grown on a collagen substrate (e.g. Table 5, col 5).

In addition, Sand, BJ teaches that human type-1 collagen molecule consists of chains of 300 nm triple helixes joined by 67nm uncoiled bands (col 10, lines 32-33). Holbrook et al teach that the dermal matrix of connective tissue is comprised of collagen, of which 80-90% is type I and 8-12% is type III, glycosaminoglycan, fibronectin, and tenascin (pg 117, col 1, para 3 & pg 119, col 1, para 1 and 3). **Biegel et al teach the use of the Transwell filters coated with hydrated collagen gels** for the use in growing endothelial cells in vitro which resulted in monolayers growing until confluency and exhibiting biochemical, morphological, and electrophysiological properties reflective of cells in vivo (abstract).

Therefore in light of Bell, Parenteau, Sand, Holbrook and Biegel et al it would have been obvious to one of ordinary skill in the art to make a cultured tissue construct comprising fibroblast cells, such as neonate male foreskin or dermal, grown under a sequential cell culture conditions on a Transwell plate coated with collagen to produce a layer of extracellular matrix comprising type I and III fibrillar collagen, glycosaminoglycan, decorin, fibronectin, and tenascin and wherein said cells are cultured in the absence of exogenous matrix components in a chemically defined media containing no non-human components and comprising a second layer of epithelial cells, such as keratinocytes; and utilizing said construct for transplanting in an animal model. Furthermore, Parenteau teaches that cells can be cultured on glass or plastic, and in the absence of exogenous matrix components like collagen. Parenteau et al also teach the culturing of human karatinocytes on plates NOT coated with collagen (col.24, example-5). Furthermore the percentage of cell confluence, the thickness of the resulting matrix, and the density of the seeded cells are rate effective variables which one of ordinary skill in the art could readily ascertain through routine experimentation.

One would have been motivated to utilize a tissue construct in the absence of exogenous matrix components to provide an efficacious method of dermal regeneration, which did not require the construction of a biodegradable matrix, and to utilize a chemical defined medium to optimize tissue differentiation and growth (Parenteau et al, col 1, lines 35-55). One would also have been motivated to use a porous membrane, such as Transwell plates, because the layer of collagen (or polycarbonate membrane) on the plates would allow for the efficacious adhesion and differentiation of fibroblast cells, especially in light of the absence of an exogenous extracellular matrix scaffold. There would be a reasonable expectation of success because Bell demonstrated that tissue constructs could be generated utilizing a base layer of fibroblasts with a top layer of keratinocytes to generate full thickness skin grafts and done in the absence of three dimensional matrices (e.g. Bell, claim 16) and because Parenteau et al had demonstrated the successful use of tissue constructs comprising keratinocytes using said defined culture medium and in a sequential two step culture system and without any collagen coating and because Biegel et al had demonstrated the successful use of the Transwell system for in vitro growth and differentiation of endothelial cells into tissue (e.g. Parenteau et al, Example 5, col 24, lines 35-40, & Biegel et al, abstract).

Claims 1, 4, 5, 9, 13, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jahoda et al (1993) in view of Parenteau et al (US Patent 5,712,163) for the same reasons of record as set forth in the official action mailed on 07/03/01.

The applicant argues that Jahoda does not teach the creation of a cultured tissue construct comprising cells grown under conditions to produce a layer of extracellular matrix, which is synthesized and assembled by the cultured cells (response, page 9, ¶ 2). The applicant further argues that Parenteau does not teach absence of exogenous matrix components and synthetic components. Applicant further argues that Parenteau does teach a chemically defined cell culture medium but does not teach or suggest instantly claimed invention. The applicant further argues that the ability of fibroblasts cells to produce layer extracellular matrix which is synthesized and assembled by cultured fibroblasts in the absence of exogenous matrix component or synthetic members was unexpected (response, page 9-10).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The applicant fails to consider the combined teaching of the reference cited herein in entirety. The combination and modification of the teachings of the prior art clearly suggested the claimed invention.

In this case, Jahoda et al teach that the transplantation of dermal papilla cells in rat ear wounds resulted in the production of hair growth in comparison to a control of transplanted skin fibroblasts, which resulted in no new hair growth (abstract and pg 585, col 1, para 1-3 and Table 1). Although, Jahoda et al does not teach the use of a cultured tissue construct system grown in vitro to produce extracellular matrix components, Parenteau would have cured this deficiency.

Parenteau et al teach the use of a chemically defined cell culture medium, which by definition are absent of undefined proteins from protein supplements such as serum, and wherein the cell culture systems comprise said cell culture medium and a substrate for the cells, such as glass or plastic, and in the absence of exogenous matrix components or synthetic membranes which resulted in the prolonged growth and differentiation of cells, such as keratinocytes,(e.g. col 1, lines 35-55, claims 20 and 24). Parenteau clearly teaches the culturing of human karatinocytes on plates NOT coated with collagen (col.24, example-5). Parenteau et al also teach the method of producing skin equivalents grafts in vitro utilizing keratinocytes and dermal (fibroblast) equivalents (example 6, col 25, line 61-col 26, line 14), and the use of a sequential two culture medium process in the absence of a substrate which showed only a slight decrease in plating efficiency in comparison to those that were grown on a collagen substrate (e.g. Table 5, col 5).

Thus in light of Jahoda and Parenteau et al, it would have been obvious to one of ordinary skill in the art at the time of the invention to create a cultured tissue construct comprising dermal papilla cells with fibroblast cells and with or without a top layer of epithelial cells, such as keratinocytes. One would have been motivated to do this to provide a method of producing a tissue construct that could be used to generate new hair growth (Jahoda et al, Table 1). There would be a reasonable expectation of success because Jahoda et al demonstrated the ability to culture dermal papilla cells and transplantation of the dermal papilla cells onto rats for successful production of hair. In addition to culturing and implantation of fibroblasts for successful production of dermal skin, Parenteau further demonstrated the ability to culture keratinocytes in the absence of exogenous matrix components and synthetic membranes to produce differentiated, stratified tissue (Parenteau et al, abstract). Thus the invention as claimed is *prima facie* obvious in view of prior art of record

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PRIMARY EXAMINER